REMARKS

Present Status of the Application

This is a full and timely response to the advisory Office Action mailed on May 18, 2010. In the advisory Office Action, the Office refuses to enter the amendments and the evidences filed after the final Action as further consideration and/or search may be required, and the Office maintains its rejections to claims 19-21 and 23 under 35 U.S.C.§ 112, first paragraph for failing to comply with the enablement requirement.

Applicant has amended claim 19 to more clearly define the invention. It is believed that the amendments are supported by the original specification and drawings of this application, and no new matter is added by way of these amendments made to the claims or to the application. After entry of the foregoing amendments and considering the following remarks, reconsideration and allowance of the claims are respectfully solicited.

Discussion of 35 U.S.C. §112, 1st paragrah rejections

Claims 19-21 and 23 were rejected under 35 U.S.C. 112, first paragraph for failing to comply with the enablement requirement.

More specifically, the Office Action considers that the specification enables a method of promoting regeneration and reconnection of damage neural pathways in a mammal comprising the administration of an effective amount of SEQ ID NO:3, but not enabling such method comprising the administration of an effective amount of at least one oligonucleotide having a

sequence at least 80% identical to a sub-sequence of SEQ ID NO:1 comprising 8 to 50 nucleobases.

In this Response to the Office Action, the phrase "*a region of the mRNA encoding Transforming growth factor β receptor II which is a "loop" or "bulge" and which is not part of a secondary structure*" has been deleted from claim 19. Claim 19 has now been amended to refer to at least one oligonucleotide having a sequence, wherein the sequence is directed to the region encompassing the translation initiation codon of the ORF of the gene encoding TGF-βR_{II}.

In brief, Applicant respectfully submits that SEQ ID NO:1 is the complete antisense sequence that are complementary to the gene encoding TGF-R_{II} (i.e. TGF-R_{II} gene). SEQ ID NO:3 is the sequence of the oligonucleotides 86729-86744 of SEQ ID NO:1. Therefore, SEQ ID NO:3 is the antisense oligonucleotide complementary to a specific region of the gene encoding TGF-R_{II} (i.e. the region encompassing the translation initiation codon of the ORF of the gene encoding TGF-R_{II}).

The translation initiation codon (start codon) usually has the DNA sequence ATG. SEQ ID NO:1 is an antisense sequence of the whole gene of the TGF-βR_{II}. Thus, the sequence of the start codon has to be translated into the complementary sequence and the direction of the resulting sequence has to be rearranged from 3' to 5' to corresponds to the conventional direction of 5' to 3'. Accordingly, the resulting sequence of the start codon corresponding to an antisense sequence becomes CAT, and this CAT is found in SEQ ID NO:1 at position 86,742-86,744 (corresponds to 86,741 – 86,743 of the Examiner's numbering). The fact that this CAT is the

start codon of the TGF-βR_{II} gene may be found at the nucleotide database of the EMBL at the following web site.

http://ensembl.org/Homo_sapiens/Transcript/Sequence_cDNA?g=ENSG00000163513;t=ENST00000295754

The aforementioned database entry shows that cDNA sequence of the TGF-βR_{II} gene with the start codon ATG at position 383. Since a whole gene and a cDNA have different length, the numbering between SEQ ID NO:1 and the cDNA sequence of the TGF-βR_{II} differs. However, the consistency of the position of the start codon CAT in SEQ ID NO:1 and start codon ATG in the cDNA sequence of the TGF-βR_{II} can be clearly identified by comparing the sequences adjacent to the start codon (please note: to transform coding DNA sequence into an antisense sequence as explained above).

The start codon usually is the beginning of the ORF.

Claim 19 relates to oligonucleotides having a sequence at least 80% identical to a sub-sequence of SEQ ID NO:1 comprising 8 to 50 nucleobases, wherein said sequence is capable of hybridizing sufficiently with the region encompassing the translation initiation codon of the open reading frame of the gene encoding transforming growth factor β receptor II. This implies that the region encompassing the start codon of the ORF of the TGF-βR_{II} spans from 8 to 50 nucleobases upstream from the start codon to 8 to 50 nucleobases downstream from the start codon.

The SEQ ID NO: 3 is positioned within SEQ ID NO:1 at nucleobases 86,730 – 86,745 (corresponds to 86,729 – 86,744 of the Examiner's numbering). This position in SEQ ID NO:1 clearly includes 86,729 – 86,744 of the start codon CAT of the TGF-βR_{II} gene. In addition, this position of SEQ ID NO:3 within SEQ ID NO:1 is also located within the region spanning from 8 to 50 nucleobases upstream from the start codon ATC to 8 to 50 nucleobases downstream from the start codon ATC. Thus, SEQ ID NO: 3 is definitely located at the position of the start codon of the TGF-βR_{II} gene as represented by SEQ ID NO: 1. And SEQ ID NO:3 is definitely directed to a region encompassing the translation initiation codon of the ORF of the gene encoding TGF-βR_{II} as claimed in claim 19. Accordingly, claim 19 refers to oligonucleotides that encompass SEQ ID NO: 3.

The oligonucleotides, as claimed in the currently pending claim 19, encompass SEQ ID NO: 3 or contain a part of SEQ ID NO: 3 TGF-βR_{II}, and SEQ ID NO: 3 has proven its activity in promoting successful regeneration and functional reconnection of damaged neural pathways in Examples 6-8 of the present application, the oligonucleotides as claimed in the currently pending claim 19 will demonstrate the same activity as SEQ ID NO: 3. Accordingly, the oligonucleotides and their activity according to claim 19 may be regarded as being very well supported by the specification of the application and the enablement requirement is fulfilled.

The Examiner again cites Ogorelkova et al. and argues that sequences other than SEQ ID NO: 3 will not necessary show the same activity as SEQ ID NO: 3 unless this is proven by experimental data. Applicant traverse the Examiner's assertion for at least the following reasons.

Ogorelkova et al. tested a set of adenovirus-delivered antisense RNA fragments and adenovirus-delivered shRNH-molecules for their ability to target TGF-βR_{II}. Ogorelkova et al. used a dicistronic reporter, consisting of the coding sequences for TGF-βR_{II} and green fluorescent protein (GFP) to screen for optimal silencing agents targeting TGF-βR_{II}. The activity of the antisense molecules was tested with cells transfected with the reporter, thus with exogenous TGF-βR_{II} gene, and with cells without reporter, thus with endogenous TGF-βR_{II} gene. The results of Ogorelkova et al demonstrate that the antisense RNAs were able to silence exogenous TGF-βR_{II} but were unable to silence endogenous TGF-βR_{II}. In contrast, the shRNAs were able to silence exogenous and endogenous TGF-βR_{II}. Thus, from an activity on exogenous genes, it can not be concluded whether there might be the same activity on endogenous genes. But this result is of no relevance for the situation of the present application. The present application does not claim the ability to predict the activity of an antisense compound on the basis of a cell culture assay. The present application has proven that the antisense oligonucleotides containing SEQ ID NO: 3 demonstrate a claimed therapeutic activity in an in vivo animal model.

In addition, Ogorelkova et al. present that antisense RNA or shRNA molecules with different but similar sequences show similar results for silencing TGF-βR_{II} gene. For example, RNA molecules A, B and D included all the sequence of D and showed a similar extent of reduction of GFP fluorescence of the reporter construct (page 6, right column). This means that RNA molecules A, B, and D showed a similar extent of silencing of exogenous TGF-βR_{II} gene.

Further, shRNA molecules 1, 2, 3 and 4 contain similar sequences and all four scored positive for GFP reduction and were able to reduce expression of both transfected and endogenous TGF-βR_{II} (page 12, left column, paragraph 2). Therefore, in contrast to the statement of the Examiner, Ogorelkova et al., in essence, supports Applicant's opinion that the oligonucleotides according to claim 19 show all the same activity of SEQ ID NO: 3 because they contain SEQ ID NO: 3 or a part of SEQ ID NO: 3. Therefore, the oligonucleotides and their activity according to claim 19 may be regarded as being fully supported by the specification of the present application and the enablement requirement is fulfilled.

Furthermore, it has to be emphasized that the intention of Ogorelkova et al. was not to show that it might be difficult to select effective antisense sequences. The object of Ogorelkova et al. was to investigate whether it is possible to deduce from positive results of antisense RNAs on exogenous genes that the same antisense RNAs will be also efficient on endogenous genes.

The paragraphs in Ogorelkova et al., cited by the Examiner, are parts of the abstract and the introduction. Ogorelkova et al. state that the selection of efficient antisense RNA might be difficult only in context with the previously tried methods. Ogorelkova et al. chose a different method based on reporter transgene targets and state in page 3, left column, second paragraph, that the use of reporter transgene targets may, therefore, facilitate the selection of efficient silencing molecules. Thus, the experimental results of Ogorelkova et al. must be interpreted in connection to the methods they used and the suitability they found for these methods. Hence, the specific experimental results should be of more importance than a general statement made in an introduction. Additionally, the experimental results of Ogorelkova et al. clearly show that a

conclusion from the efficiency of a specific RNA molecule to the efficiency of a similar RNA molecule is possible.

In light of the foregoing amendments and for at least the reasons set forth hereinbefore, Applicant respectfully submits that the 35 U.S.C. 112, 1st paragraph rejections have been traversed and/or rendered moot, and withdrawal and reconsideration of the rejections are respectfully requested.

CONCLUSION

For at least the foregoing reasons, it is believed that the pending claims of the present application patently defines over the prior art and are in proper condition for allowance. If the Examiner believes that a telephone conference would expedite the examination of the above-identified patent application, the Examiner is invited to call the undersigned.

Respectfully submitted,
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Date: July 16, 2010

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